

suppressant of B cell responsiveness. The Examiner further contends that Nakamura et al. teach an antibody that binds to the extracellular domain of the transducer component and observes downstream events that would allegedly be a consequence of causing a dissociation or inhibiting an association of the extracellular ligand binding component and the transducer component. Therefore, the Examiner concludes that, taking Nakamura et al. as a whole, there does not appear to be a patentable distinction between the claimed and referenced methods.

Applicants traverse the Examiner's contention that Nakamura et al. anticipate the claimed invention. As stated in the previous response, Applicants submit that the antibody of Nakamura et al., although it binds to the Ig β transducer component, did not induce receptor desensitization and was unable to prevent stimulation of B cells by an anti-IgM antibody (see Fig. 3), which indicates that the receptor components could associate with one another in the presence of the anti-CD79b antibody. In this response, Applicants submit that this conclusion is supported by all of the experiments in Nakamura et al., including the one referenced by the Examiner in section 3.4 (page 43). Contrary to the Examiner's assertion that this experiment shows that anti-CD79b suppresses a B cell response and that the method meets the limitations of the claimed methods, Applicants submit that Nakamura et al. explicitly state in the Discussion section that the CD79b antibody does not induce B cell unresponsiveness, including in the experiment described in section 3.4. Therefore, Nakamura et al. verify Applicants' position.

First, Applicants respectfully refer the Examiner to the discussion on page 43, last full paragraph, where Nakamura et al. set forth 3 possible mechanisms for suppression of B cell responses by CD79b. The first mechanism is by down-modulation of B cell receptor expression (i.e., the receptors are still responsive, but the number of receptors expressed by a B cell is reduced), which does not read on the present claims. The second mechanism refers to a mechanism which has been long-recognized in the art, whereby saturation of the B cell receptor on late differentiating B cells (e.g., just prior to development into antibody-secreting cells), such as by antigen binding or antibody binding (i.e., stimulation), interferes with the final differentiation of the B cell, such that antibodies are not secreted. This mechanism is also clearly distinct from the mechanism by which the claimed antibody acts. The third mechanism is induction of B lymphocyte unresponsiveness.

As the present inventors have shown, one means by which B cell unresponsiveness is induced is by dissociation of the extracellular binding component and the transducer component.

It is submitted that Nakamura et al. clearly conclude that, of the three proposed mechanisms, only the first two (i.e., down-modulation of BCR or interference with differentiation, and not B cell unresponsiveness) were induced by anti-CD49b (see the paragraph bridging pages 43 and 44). Nakamura et al. go on to state in the second column of page 44 that they "could not induce unresponsiveness of small resting B lymphocytes by anti-CD79b antibody". Finally, on page 45, paragraph bridging columns 1 and 2, Nakamura et al. specifically address the experiment from section 3.4 referenced by the Examiner and state that the inhibitory effect in that experiment "is caused by down-modulation of BCR and inhibition of B lymphocyte differentiation, and not by induction of B lymphocyte unresponsiveness" (emphasis added). Therefore, the authors of the reference cited by the Examiner explicitly contradict the Examiner's conclusion regarding the teachings of the reference.

Therefore, it is again submitted that failure of the antibody of Nakamura et al. to induce receptor unresponsiveness or to prevent receptor stimulation shows that the antibody of Nakamura et al. does not cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component. Indeed, the mechanisms of suppression of B cell responses observed by Nakamura et al. are likely to be associated with a stimulatory effect of the antibody. Therefore, Nakamura et al. fail to teach each and every element of the claimed invention.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 4-6, 10, 18 and 33 under 35 U.S.C. § 102(b).

Rejection of Claims 1, 4-6, 9-10, 18-19, 21-22, 30-31 and 33 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 4-6, 9-10, 18-19, 21-22, 30-31 and 33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Ways et al. in view of Nakamura et al. and further in view of Vilen et al. Specifically, the Examiner again asserts that one of skill in the art would have been motivated to substitute the antibody of Nakamura et al. for the PKC inhibitor used in the method of Ways et al. for treating autoimmune disease because one would have recognized that the antibody that acted upstream of the PKC inhibitor would be more efficacious than an

inhibitor of PKC to block B cell activation. Moreover, the Examiner submits that Vilen et al. teach that long term B cell unresponsiveness is independent of PKC activation which would allegedly cause one of skill in the art to expect that the antibody would be more effective than the PKC inhibitor. The Examiner maintains the position that the combination of references make the present invention *prima facie* obvious.

Applicants traverse the Examiner's rejection of Claims 1, 4-6, 9-10, 18-19, 21-22, 30-31 and 33 under 35 U.S.C. § 103.

First, it is noted that for a *prima facie* case of obviousness to be proper, the combination of references must teach or suggest every limitation of the claimed invention. Referring to the discussion of Nakamura et al. above, it is again submitted that Nakamura et al. fails to teach or suggest the production and use of an antibody that binds to the transducer component of a B cell antigen receptor (i.e., the Ig α -Ig β dimer) to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component, and that does not substantially stimulate the B cell antigen receptor. Ways et al. and Vilen et al. each fail to teach an antibody, as the Examiner has acknowledged. Therefore, the combination of references fails to teach the antibody recited in the present claims and as such, the *prima facie* case for obviousness fails.

Moreover, Applicants again assert that the connection of Ways et al. with either of Vilen et al. or Nakamura et al. is not based on any reasonable motivation provided by any of the references. First, as set forth previously, the method of Ways et al. refers to a completely distinct method of suppressing B cell function which operates by a different mechanism and which is an intracellular means of manipulating a B cell response. Ways et al. is directed to this particular method and therefore does not provide the motivation to look to other methods of manipulating a B cell response. The Examiner contends that a teaching of Vilen et al. that long term B cell unresponsiveness is independent of PKC activation would lead one to substitute an antibody which allegedly induces long term unresponsiveness. Applicants submit that this is illogical, since a teaching by Vilen et al. that B cell unresponsiveness is independent of PKC activation would more reasonably lead one to avoid or ignore the teachings of Ways et al., not to modify them. In summary, Applicants submit that the combination of references, even when viewed as the Examiner has considered it, does not provide any motivation to substitute an antibody into the method of Ways et al.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 4-6, 9-10, 18-19, 21-22, 30-31 and 33 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the issues raised by the Examiner in the August 8, 2001 Office Action and submit that the claims are in a condition for allowance. The Examiner is encouraged to contact the below-named agent to discuss any remaining questions or concerns regarding Applicants' position.

Respectfully submitted,

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